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EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	10

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/070,305	Applicant(s) JONAS ET AL.	
	Examiner Mark L. Berch	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5 and 7-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-3,5,7-9,11,12, 19, 21 and 22* is/are allowed.

6)☒ Claim(s) *10,13-18 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for potency disorders, does not reasonably provide enablement for cardiovascular disorders generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. Owing to the fairly wide range of X choices, and the large number of substituents, the genus covers millions of compounds.

(b) Scope of the diseases covered. Cardiovascular disorders embraces a vast array of problems, some of which are contradictory to others. This covers various forms of endocarditis, including Verrucous, Atypical verrucous (Libman-Sacks) Non-bacterial thrombotic - NBTE (marantic), bacterial, viral, and rickettsial endocarditis. It covers different forms of atresia, including tricuspid atresia without TGV, pulmonic valvular atresia and aortic atresia. It includes assorted cardiomyopathies, including restrictive cardiomyopathy, peripartum cardiomyopathy, hypertrophic cardiomyopathy, and congenital cardiomyopathy. It embraces various forms of aortic Stenosis, including valvular aortic Stenosis, idiopathic hypertrophic sub-aortic stenosis (IHSS), subvalvular aortic stenosis, and supravalvular aortic stenosis. There are all kinds of miscellaneous syndromes, including subclavian steal syndrome, Eisenmenger syndrome, mitral valve prolapse (Barlow) syndrome, Aortic arch syndrome, scimitar syndrome, hypoplastic left heart syndrome, Lutembacher syndrome, and superior vena cava syndrome. It covers various forms of hypertension, including primary (idiopathic) pulmonary hypertension, neonatal pulmonary venous hypertension and pulmonary hypertension. It includes aortic aneurysms, including both thoracic and abdominal, as well as mycotic aneurysm. It covers various types of arrhythmias and atrial fibrillation. It covers elevated blood levels of triglycerides, of total cholesterol or of LDL cholesterol, and hyperlipoproteinaemias. It covers different forms of ischaemic heart disease including congestive heart failure and myocardial infarction. It covers a vast array of structural

defects such as atrial septal defect (ASD), aorticopulmonary window, egg-on-its-side heart, gooseneck deformity, endocardial cushion defect, arc of Buehler, arc of Riolan, truncus arteriosus, Ebstein's Malformation, azygos continuation of interrupted IVC, Atrioventricular Canal, ventricular septal defect (VSD), abdominal aortic coarctation, aortic pseudo-coarctation, complete endocardial cushion defect, Hypoplastic Left Heart, patent ductus arteriosus (PDA), congenital absence of pulmonary valve, aortic coarctation partial endocardial cushion defect, Single Ventricle, box-like heart, pulmonary sling, Left Ventricle to Right Atrial Shunt, total anomalous pulmonary venous return (TAPVR), partial anomalous pulmonary venous return (PAPVR), and transposition of the great vessels. It covers certain peripheral vascular disorders, such as deep-vein thrombosis and thrombophlebitis and assorted cerebral vascular diseases including migraine. There is hypotension, which can arise from all sorts of other problems. All there is a huge collection of other cardiovascular problems, including thymoma (invasive and non-invasive), admixture lesion, left ventricular hypertrophy, tortuous aorta, aortic laceration pulmonary artery sarcoma, aortic regurgitation, pneumomediastinum (Spontaneous and traumatic), middle mediastinal mass, posterior mediastinal mass, Uhl disease, right ventricular hypertrophy, cardiac rhabdomyoma, acute aortic dissection, pericardial cyst, carotid artery bruit, pulmonary embolism, venous angioma, varicose veins and spider veins, congenital heart disease, pericardial effusion, tetralogy of Fallot, coronary artery calcification, endocardial fibroelastosis, fibromuscular dysplasia (FMD), thromboangiitis obliterans (Buerger disease), left or right ventricular volume overload, Takayasu arteritis, situs inversus, neonatal heart failure, myocarditis, arteriosclerosis, atherosclerosis, stroke and many others.

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The dosage range information provided on page 13 is completely generic as to disease. That is, it in effect provides the same dosage for any of dozens of disorders.

(4) State of the Prior Art: The invention provides for certain types of benzylamino pyrazolo[4,3-d]pyrimidines. So far as the examiner is aware, no benzylamino pyrazolo[4,3-d]pyrimidines have been used for any of these disorders.

(5) Working Examples: There are no working examples to the treatment of any disorder. Indeed, the specification provides no biological data whatsoever.

(6) Skill of those in the art: The skill level in the art of pharmacological treatment of cardiovascular disorders varies with the disorder. In some areas such as hypertension it is relatively high. But in the great majority of cases it is very low as the disorders cannot be treated with pharmaceuticals. The vast majority are treated either by surgical means or cannot be treated at all, leaving only general management of symptoms.

(7) The quantity of experimentation needed: Owing to factors (1), (3) and (6), the quantity of experimentation is expected to by high.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

The traverse is unpersuasive. Applicants first raise issues of reason to doubt. This was set forth above. Most things within the scope of this claim language have never been treated with any pharmaceuticals, and this is ample reason to doubt.

Applicants next cite *Houghton*, *Citron* and *Eltgroth*. These cases all dealt with 35 USC 101.

It is correct that the compounds are enabled. As was stated previously, the compounds are enabled for potency disorders, and only one utility is needed to enable the compounds.

Applicants argue that "through routine screening and testing" one could determine "which of the synthesized compounds ... possesses beneficial properties to any of the specific diseases" encompassed by the claims. The claim recites that all compounds are to be used for all such conditions. Moreover, this is not the proper standard. As was stated in *In re Gardner, Roe, and Willey*, 166 USPQ 138 at 141 (CCPA 1970), "... our view is that the law requires that the disclosure in the application shall

inform them how to use, not how to find out how to use for themselves." Third the screening that applicants refer to does not exist for the scope of this claim. For e.g. endocardial cushion defect, arc of Buehler, arc of Riolan, and truncus arteriosus, there are no screening tests for drugs to treat these.

Applicants next point to page 2, lines 20-39. This makes no mention of any Cardiovascular diseases or indeed any diseases at all.

Applicants next state that the specification provides "guidance as to the type of activity the claimed compounds possess." But the language there --- "diseases in which an increase in the cGMP ... level leads to inhibition or prevention of inflammation and muscle relaxation." --- is not the claim language. The claim language of Cardiovascular is both narrower and broader than that.

Applicants argue "The Office Action also alleges that no specific biological data is provided, i.e. there are not working examples to the treatment of any disorder. However, the law does not require an applicant to test a compound in examples." The examiner has not said that the law so requires, nor has the examiner made any such requirement. However, the existence of working examples is, under *Wands*, a proper factor to be considered among many others to determine if the compounds are enabled. It does not "turn on" whether there are examples, but the absence of any biological data and the absence of any working examples to any actual disorder is a proper factor to consider. Applicants cite *Brana* in this regard. In *Brana*, there was biological testing data.

Applicants cite *Cross v. Iizuka* concerning the correlation between *in vitro* and *in vivo* results. In that particular case, there was established to be just such a correlation.

In this case, not only have applicants not actually performed any *in vitro* tests, but they have not identified what *in vivo* tests they are talking about. Further, there are not tests predictive for "Cardiovascular diseases" because that is an extremely diverse group, some of which contradict others. For example, some have blood pressure which is too high, while others have blood pressure which is too low, and still others have no effect on blood pressure at all.

With regard to the dosage, this cannot be determined without undue experimentation, since there are dozens of disorders to consider, many of which have never been treated with pharmaceuticals, and hence there is no general guidance to go on in terms of the particular disorder. The only daily dosage information provided is a page 13, line 8. But that is not linked to any particular disorder, and thus is largely worthless. Moreover, the range is so large --- 500 fold --- that it is of little practical value (note *Gardner*, where a much smaller range was still held to be of little value). In this regard, applicants refer to *Bundy*, saying that this is "a case having similar facts to the current case." The facts in that case were radically different, because in Bundy, 1) it was a compound being rejected, not the method (that very distinction was made specifically in the Court decision at the sentence bridging pages 51-52) 2) the genus was much smaller and 3) the compounds were prostaglandins, a well known class of compounds whose uses were well established.

Arguments about claims allowed on the basis of different specifications are of no value.

MPEP 2164.05 states, "Once the examiner has weighed all the evidence and established a reasonable basis to question the enablement provided for the claimed

invention, the burden falls on applicant to present persuasive arguments, supported by suitable proofs where necessary" that the claims are indeed enabled. Applicants have not met that burden.

Claims 13-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds and salts, does not reasonably provide enablement for solvates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The dozens of examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here: there is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

The traverse is unpersuasive. Applicants argue that all those failures were meaningless because the examples "were not directed to the preparation of solvates." The examiner disagrees. These failures provide ample reason to doubt. One does not direct a synthesis toward solvates; the solvates either form or they do not form. In this case, the evidence of record is that these compounds do not form solvates.

With regard to *Houghton*, *Citron* and *Eltgroth*, these cases all dealt with 35 USC 101.

Applicants then argue that a specification preferably omits what is well known in the art. What exactly does this refer to? That is, what well-known but omitted facts do applicants seek to rely on in this regard? Similarly, applicants argue that "not every last detail is to be described" --- again, what detail is it that applicants refer to here? Applicants then argue that one can prepare the solvates without undue experimentation. How? If the compounds of e.g. example 2 did not form a hydrate, how do applicants plan to force it to do so?

Claims 1 and 3-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 7, who is in need thereof? Is everyone in need of this, or just certain people, and if the latter, who? Determining whether a given disease responds or does not respond to such inhibition will surely involve undue experimentation. Suppose that a given Inhibitor X when administered to a patient with Disease D does not obtain a response. Does one then conclude that Disease D does not fall within this claim? Keep in mind that:

A. It may be that the next patient will respond. It is quite common for pharmaceuticals to work only with some people, not all. Thus, how many need to be tested?

B. It may be that the wrong dosage or dosage regimen was employed. It is quite common for pharmaceuticals to work at one dosage, but not at another which is

significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? Thus, how many dosages and dosage regimens must be tried before one is certain that this pharmaceutical won't affect Disease D?

C. It may be that X simply isn't potent enough for Disease D, but that another inhibitor Y is potent enough, so that D really does fall within the claim. Thus, how many different inhibitors must be tried before one concludes that D doesn't fall within the claim?

D. Conversely, if D responds to Y but not to X, can one really conclude that D falls within the claim? It may be that the X result is giving the accurate answer, and that the success of Y arises from some other unknown property which Y is capable of. Thus, when mixed results are obtained, how many more pharmaceuticals need be tested?

E. Finally, suppose that X really will work, but only when combined with Z. There are for example, agents in the antiviral and anticancer technology which are not themselves effective, but the disease will respond when the agents are combined with something else.

F. In addition, literally speaking, any disorder can be treated with any drug, although the treatment might not be successful. Assuming that "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000?

As a result, determining the true scope of the claim will involve extensive and potentially open-ended research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

Claims 15-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. R5 as phenyl or phenylmethyl is not described in the specification. Page 1, line 19 requires that the three variables be "monosubstituted by R8" Note that R8 cannot be H. These two choices are not substituted at all as claim 15 is written and must be removed. The same is true for the cyclohexyl in claim 18. These all need to have an R8 substituent attached. For the same reason, these claims are objected to as improperly dependent on claim 1, as claim 1 does not provide for them.

Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is likely that "are" at next to last line of claim 20 should be "is".

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 703-308-4718. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 308-4716. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 708-308-1235.

Mark L. Berch
Primary Examiner
Art Unit 1624

October 15, 2003